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RESEARCH ARTICLE

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Fetal heart rate during maternal sleep

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Abstract

Despite prolonged and cumulative exposure during gestation, little is known about the fetal response to maternal sleep. Eighty-four pregnant women with obesity (based on pre-pregnancy BMI) participated in laboratory-based polysomnography (PSG) with continuous fetal electrocardiogram monitoring at 36 weeks gestation. Multilevel modeling revealed both correspondence and lack of it in maternal and fetal heart rate patterns. Fetal heart rate (fHR) and variability (fHRV), and maternal heart rate (mHR) and variability (mHRV), all declined during the night, with steeper rates of decline prior to 01:00. fHR declined upon maternal sleep onset but was not otherwise associated with maternal sleep stage; fHRV differed during maternal REM and NREM. There was frequent maternal waking after sleep onset (WASO) and fHRV and mHRV were elevated during these episodes. Cross-correlation analyses revealed little temporal coupling between maternal and fetal heart rate, except during WASO, suggesting that any observed associations in maternal and fetal heart rates during sleep are the result of other physiological processes. Implications of the maternal sleep context for the developing fetus are discussed, including the potential consequences of the typical sleep fragmentation that accompanies pregnancy.

KEYWORDS
fetal heart rate, fetus, maternal-fetal interaction, polysomnography, prenatal development, sleep

1 | INTRODUCTION

The period before birth provides the substrate for subsequent human development. A third of human gestation occurs during maternal sleep yet there is scant information on whether the fetus responds to the coordinated physiological alterations that accompany the transition from maternal wakefulness to sleep and its ensuing progression through the night. The maternal-fetal relationship is complex and multidimensional (DiPietro et al., 2006). The fetus reacts to experimental manipulations of maternal arousal during the day with changes in patterns of fetal heart rate, including in response to manipulations designed to increase arousal

(Benson et al., 1987; DiPietro et al., 2003, 2008; Fink et al., 2010; Monk et al., 2004; Werner et al., 2007) and also to induce relaxation (Akbarzade et al., 2015; DiPietro et al., 2008; Fink et al., 2011). Thus, it would be expected that maternal sleep exerts an influence on the developing fetus, and if so, variations in maternal sleep, and the fetal response to it, may have implications for ontogeny. We have had long-standing interest in documenting how the maternal context influences the developing fetus and provides the gestational foundation for subsequent postnatal development. Our proposed model of autonomic differentiation of sympathetic and parasympathetic processes during the prenatal period is based on the expression of fetal responsivity to exogenous and endogenous stimuli that impinge on or are generated from within the intrauterine environment (DiPietro et al., 2015).

Fetal heart rate and variability are the most conspicuous and accessible measures of antenatal functioning and have been well-established as proxy indicators of the developing fetal nervous system (Dalton et al., 1983; DiPietro et al., 2015; vanLeeuwen et al., 2013; Nijhuis & tenHof, 1999; Schneider et al., 2018). Diurnal rhythms were established in both fetal cardiac and motor activity in the early 1980 s, which marked the onset of intensive discovery regarding fetal neurodevelopment (Patrick et al., 1982; Visser et al., 1982). Since then, the study of variation in human fetal cardiac patterns recorded over the course of a day has continued to reveal diurnal rhythms in the third trimester with evidence of both 24 h and shorter (i.e., 8- and/or 12-hour) cycles. Fetal heart rate tends to be highest earlier in the day and declines at night, with nadirs observed in the early morning hours (Kapaya et al., 2016; Koenen et al., 2002; Lunshof et al., 1998; Sletten et al., 2018; Suzuki et al., 2001). Cyclicity in fetal heart rate variability is less well documented but, when detected, tends to show an inverse diurnal pattern with higher variability into late evening. These reports are not linked with methods to ascertain maternal sleep stage but it is reasonable to assume that the observed fetal heart rate reduction through the night occurs as women progress through sleep cycles.

To our knowledge, a single study to date reports fetal heart rate in relation to maternal sleep stages (Hoppenbrouwers et al., 1981). Data, collected in the 1970 s, relied on basic available methods of assessing maternal sleep stages and a remarkably effective method of detecting the fetal electrocardiogram (ECG) in nine maternal-fetal pairs. Results revealed no obvious associations between maternal sleep stage and fetal heart rate or variability. This report, and a related one (Hoppenbrouwers et al., 1978) were ground-breaking at the time of publication but conclusions are tempered by analytic and methodologic limitations.

Diurnal patterns of fetal heart rate tend to parallel those of maternal heart rate (Lunshof et al., 1998; Patrick et al., 1982). Within maternal-fetal pairs, when mean values are computed over an interval of time, fetuses of women with faster heart rates tend to have faster heart rates, and vice versa. Such correspondence has been found using a variety of metrics, data collection methods, and observation periods. Maternal-fetal heart rate correlations tend to be modest but significant (i.e., rs < 0.25) when computed during brief (i.e., less than an hour) recordings during the day (DiPietro et al., 2015; Zollkau et al., 2019) but higher (i.e., rs to 0.89) when based on data collected over 24 h (Lunshof et al., 1998; Patrick et al., 1982), including in a non-human primate model (Stark et al., 1999). Despite this, efforts to couple time series of maternal and fetal heart rate to reveal temporally based associations have not been successful (DiPietro et al., 2006) other than during fleeting intervals within 5-min recordings (vanLeeuwen et al., 2003). In contrast, consistent coupling between other measures (e.g., maternal skin conductance and fetal movements) has been demonstrated (DiPietro et al., 2006).

In this report, we seek to document fetal heart rate and variability over the course of the night and within each stage of maternal sleep. Data on which to base hypotheses are scant. However, a report that fetal motor activity is lower during non-REM (NREM) sleep than REM sleep (Blyton et al., 2013) suggests that fetal heart rate and variability should be lower during deep (N3) sleep, consistent with the prevailing maternal parasympathetic tone. We also evaluate the degree to which there is temporally based coupling between maternal and fetal parameters that might explain any observed associations. While prior work has failed to establish coupling in maternal and fetal heart rate, those studies were conducted during relatively short segments of maternal waking life. Maternal sleep provides a different context for characterizing the maternal-fetal relationship that is both prolonged and perhaps less subject to disruption -- thereby more likely to reveal coupling. We present maternal sleep state data generated from standard laboratory-based polysomnography (PSG) that has been integrated with continuous and concurrent fetal ECG data. This report is part of broader project aims that include evaluating the clinical issue of whether maternal sleep-disordered breathing (SDB) jeopardizes the fetus. Thus, to increase the prevalence of SDB, the sample was restricted to obese pregnant women. Findings related to maternal SDB and fetal well-being will be presented elsewhere, but sample constraints – despite the prevalence of obesity in the United States (Hales et al., 2020) – provide a threat to generalizability to this report. As a result, the contributions of both maternal obesity and level of observed SDB to any detected associations will be evaluated.

2 | METHOD

2.1 | Participants

Obese (BMI ≥ 30 kg/m^2) women carrying singleton fetuses were recruited as volunteers from the obstetric practices of a tertiary medical institution, including from a specialty clinic focused on nutritional and lifestyle management in pregnancy. Eligibility was restricted to non-smoking women with normally progressing pregnancies. The data presented here are derived from PSG recordings conducted on 107 maternal-fetal dyads during or near the 36th week of gestation. These cases reflect a subsample of a cohort of pregnant women (n = 131) who were initially eligible for PSG as part of

the study component pertaining to SDB during pregnancy but either declined PSG (n = 10), delivered prior to their scheduled sleep study or developed pregnancy complications that excluded their participation (n = 14). Of the 107 eligible women, difficulties inherent to collecting continuous fetal ECG data resulted in data of insufficient quality in 22 cases. Data from one additional participant were eliminated due to total sleep duration during the course of the study night of less than an hour. Thus, analyses are based on the remaining 84 maternal-fetal pairs with adequate signal quality throughout the night. Sociodemographic data were collected via maternal report prior to the overnight recording; infant and pregnancy outcomes were based on medical record review. The protocol was reviewed by the local Institutional Review Board and women provided written consent.

Select maternal and infant characteristics for this sample are presented in Table 1. Most of the sample self-identified as Black or African-American (90.5%); the remaining participants reported being non-Hispanic white (7%) or multiple race/Hispanic (2.5%). Approximately half (49%) of the sample was employed outside the home and most (84.5%) had attained at least a high school graduation; of those, 7% earned a bachelor's or master's degree. Slightly less than half of the participants was nulliparous (43%). There were 12 cases (14%) with gestational or adult-onset diabetes and 15 (18%) with chronic or pregnancy-induced hypertension; most (63; 75%) had neither condition, three were comorbid. With the exception of one infant born in the 36th gestational week, all were full term (i.e., ≥37 weeks). Using birth weight percentiles specific to gestational age and sex (Talge et al., 2014), most (93%) were of appropriate size for their gestational age (AGA). The remaining six infants were evenly distributed between small for gestational age (SGA) and large for gestational age (LGA). Half (50%) of the infants were female. Ten infants were transferred to the neonatal intensive care unit for temporary observation but none had congenital anomalies or other significant conditions that would warrant exclusion.

TABLE 1 Maternal and infant characteristics (n = 84)

Variable	M (*SD*)	Range
Maternal		
Age (years)	26.9 (6.3)	18–42
Initial prenatal visit (weeks)	11.2 (4.0)	5–24
Gestational age, PSG[a] (weeks)	36.2 (0.8)	34.1–38.1
Weight, 1st prenatal visit (lbs)	231.5 (45.5)	147–393
Weight, PSG[a] (lbs)	247.1 (41.8)	166–417
BMI, 1st prenatal visit (kg/m^2)	39.2 (6.2)	31.1–61.6
BMI, PSG[a] (kg/m^2)	41.6 (6.1)	32.5–63.7
Apnea-hypopnea Index (AHI)	5.9 (10.6)	0–65.7
Oxygen saturation (SpO2)	96.6 (1.2)	93.3–99.2
Infant[b]		
Gestational age (weeks)	39.3 (1.1)	36.1–41.3
Birth weight (g)	3285 (469)	2090–4670
Caesarean section delivery	43%	
5-minute Apgar score	8.8 (0.7)	5–10

[a]*Note*. At time of polysomnography (PSG).

[b]*Note*. Infant outcomes unavailable on two infants due to deliveries outside of target hospital.

2.2 | Data acquisition

2.2.1 | Maternal polysomnography

Pregnant women were assessed using standard polysomnography as recommended by the American Academy of Sleep Medicine guidelines (Berry et al., 2012). Electroencephalograms, electrooculograms, submental and pretibial electromyograms, modified V5 electrocardiogram, body position, pulse oximetry, and respiratory inductance plethysmography signals were digitized to assess sleep stage, respiratory effort, respiratory movements and leg movements. Airflow was monitored with a nasal pressure cannula and oronasal thermistor to detect apneas and hypopneas. All signals were recorded continuously using the RemLogic 1.3 N7000 data acquisition systems (Natus Medical Inc.; Broomfield, Colorado, United States). Subsequently, non-rapid eye movement (NREM) sleep stages 1, 2, 3 (N1, N2 and N3), and rapid eye movement (REM) sleep were visually scored using EEG waveform, ocular movements, and chin muscle tone in 30-s sequential epochs according to standard criteria (Berry et al., 2012). Apneas were defined as a complete cessation of airflow lasting ≥10 s, and hypopneas as a ≥30% decrease in airflow lasting ≥10 s in association with oxygen desaturation of ≥3% or an arousal (Berry et al., 2012). The Apnea-Hypopnea Index (AHI) was the number of apneas and hypopneas divided by hours of sleep.

2.2.2 | Fetal cardiac patterns

The fetal electrocardiogram (fECG), as well as the maternal electrocardiogram (mECG), were collected using the Monica AN24 (Monica Healthcare Ltd) via five disposable electrodes arrayed on the maternal abdominal wall in standard configuration that detect and extract the fetal ECG from the larger maternal ECG signal. Processing details have been previously described (Pieri et al., 2001). This small, portable and Bluetooth-enabled device has been successfully validated against fetal heart rate derived from fetal scalp electrodes during labor (Cohen et al., 2012; Graatsma et al., 2009) and with cardiotocography (i.e., Doppler detection) before birth (Kisilevsky & Brown, 2016). R-wave intervals were timed (msec) and data were downloaded in the morning from the device for further processing and quantification.

2.3 | Data merging and consolidation

Maternal heart rate, extracted by both the Monica AN24 and polysomnography, was used to synchronize data from both sources. Briefly, Monica DK software extracted 2-s average fetal and maternal heart

rate files which were imported into the RemLogic recording. Visual inspection in RemLogic was used to align the signals, which were resampled and converted to EDF files using Matlab (MathWorks) (Kemp et al., 1992). Signal alignment was accomplished using the intercept of the regressed differences against the time after the start of the recording and continued based on the regressed slope of heart rate differences throughout the night using the Matlab resample function.

Time-synchronized fetal and maternal heart rate data were joined with the polysomnography scoring, described above. Episodes of signal loss, predominantly from the fECG, were treated by linear interpolation of artifact based on physiological plausibility. Based on existing methods (DiPietro et al., 2006), this included exceeding predetermined upper and lower thresholds as well as unexpected and rapid deviations beyond acceptable limits of prior weighted averages. Missing data spanning longer than 16 continuous seconds were not interpolated due to the impaired reliability of the recovered data. Periods of missing data were further evaluated by the percentage of missingness within 60-min windows (with 20-min overlaps between adjacent windows) and those windows with more than 50% missing data were discarded from the analytic dataset. Exclusion of periods of fetal data was accompanied by exclusion of corresponding maternal data. Figure 1 illustrates the merged data that formed the basis for analysis for a single maternal-fetal pair. In it, continuous maternal (lower line) and fetal (upper line) are superimposed over background shading reflecting onset and offset of maternal wakefulness and sleep stages (refer to key).

2.4 | Statistical analysis

Analysis of fetal and maternal heart rate and variability comprised three distinct phases: 1. evaluation of trajectories during the nighttime recording; 2. comparisons between maternal waking and sleep stages; and 3. time series analyses during the night and within maternal sleep stages.

2.4.1 | Overnight trends

Change in fetal and maternal heart rate and variability during the observation window, independent of sleep stage, was evaluated by linear mixed effect models with random intercepts for each individual and random slopes for time (*R*, version 3.5.0; *R* Foundation for Statistical Computing). A spline was inserted at 01:00 to assess potential changes in slope. Fetal and maternal values were further aggregated into 60-s non-overlapping windows; mean heart rate (fHR and mHR) and variability (i.e., standard deviations; fHRV and mHRV) were computed. The analytic time period was restricted to 21:00 to 05:00 which includes both the period of wakefulness prior to sleep onset (WPSO) and most of the night of sleep for most participants. Evaluation of the effect of sleep onset on maternal and fetal measures was based on data aligned with the onset of sleep for each participant, independent of clock time. Linear mixed effect models, based on up to 30 min of wakefulness prior to sleep onset and 30 min of data post-sleep onset, quantified in 60-s non-overlapping intervals, were used to evaluate potential changes in maternal and fetal parameters that coincided with onset of maternal sleep.

2.4.2 | Comparison of mean values by maternal sleep stage

fHR and mHR were computed within each maternal sleep stage (NREM stages N2 and N3, REM), maternal wakefulness prior to sleep onset (WPSO), and subsequent epochs of maternal nocturnal wakefulness after sleep onset (WASO). Heart rate variability was quantified in two ways: (1) the standard deviation of fHR (fHRV) and mHR (mHRV) computed within each sleep stage; and (2) for fHR only, as episodic excursions from baseline using standard criteria for transient increases and decreases in fHR. These include accelerations (i.e., 15 bpm above baseline for 15 s) and decelerations (i.e., 15 bpm below baseline for 15 s)

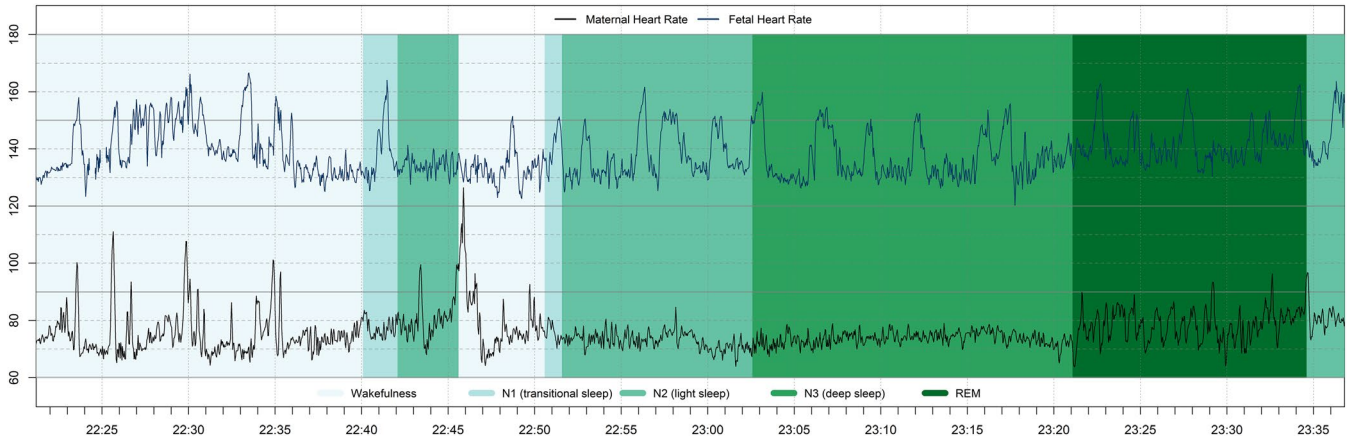

FIGURE 1 Example of continuous fetal (upper line) and maternal (lower line) heart rate data superimposed over maternal sleep staging denoted by background color (see key). This segment was collected at the onset of sleep and spans 22:22 to 23:36. Note progression from pre-sleep wakefulness (WPSO) to transitioning among sleep stages N1 and N2, intersected by a period of post sleep onset wakefulness (WASO), and ultimately to N3 and REM sleep. Large excursions in fetal heart rate reflect commonly occurring events referred to as accelerations.

displayed in each sleep stage. Instances of the latter were confirmed by visual inspection. Accelerations and decelerations are count variables so were prorated by the duration of sleep stages.

Separate linear mixed models with random effects at the subject level to account for the expected within-subject associations were fit for each dependent fetal (fHR, fHRV, accelerations) and maternal (mHR, mHRV) variable using *XTMIXED* in Stata (version 16.1, StataCorp.). A principal benefit of a random intercept model is that it accounts for variation in heart rate measures within individuals while estimating group differences. Maternal sleep stage was used as a categorical predictor with five levels (WPSO, WASO, N2, N3, and REM) for each mixed model. Pairwise post-estimation comparisons were conducted to ascertain differences in means of dependent measures across sleep stages.

2.4.3 | Maternal-fetal coupling

The maternal and fetal time series, sampled at 1 Hz, denoted as series x_m and x_f were evaluated during the full night PSG recording and during WPSO, NREM (N2 and N3 were concatenated to allow for longer segments), REM, and WASO. Two approaches were implemented: the first incorporated all data points for all 30-s epochs with different sleep stages; the second included all non-overlapping segments of the same sleep stage that lasted for at least 5 min. Below, we describe the analysis for the second approach, and the same procedure holds for the first approach. For the k-th subject and each segment evaluated, coupling between fHR and mHR was analyzed assuming that fHR and mHR are the outcomes of stochastic processes that are stationary within each segement. For a time shift s, which takes values ranging from −50 to +50 s, fHR was shifted by s seconds so that the mHR at time t was aligned with the fHR at time $t + s$. Segments that are 5 min long, for example, yield maternal and fetal HR time series of 300 data points, a pair of maternal HR, $y_m \in \mathbb{R}^{300}$, and fetal HR, $y_f^s \in \mathbb{R}^{300}$.

In addition to the procedure described above for the full night analysis, an additional approach was undertaken to determine whether there was coupling only when mHR or fHR were at their highest or lowest values by computing the first and third quartiles of y_m, denoted as Q_{25} and Q_{75} respectively. For $i = 1, \cdots, 300$, if the $y_m(i)$ was greater than the Q_{75} or less than Q_{25}, that mHR was viewed as having a large variation and $y_m(i)$ was replaced by 1; otherwise, it was viewed as having a small variation and it was replaced by 0. The same procedure was applied to y_f^s, and we obtained a new pair of time series with only 0 and 1 indicating the high and low heart rate variability (i.e., deviation from the interquartile range).

For each approach, the cross-correlation between y_f^s and y_m was computed as:

$$r(s) = \frac{\sum_{l=1}^{300}(y_f^s(l) - \overline{y_f^s})(y_m(l) - \overline{y_m})}{\sqrt{\sum_{l=1}^{300}(y_f^s(l) - \overline{y_f^s})^2 \sum_{l=1}^{300}(y_m(l) - \overline{y_m})^2}},$$

where $\overline{y_f^s}$ means the sample mean of y_f^s and $\overline{y_m}$ means the sample mean of y_m. Note that the common definition of correlation between mHR and fHR is the cross-correlation when the shift is 0. The shift captures the possible influence of mHR on fHR or the other way, depending on the sign of the shift. As a result, 100 cross correlations, $r(-49), \cdots, r(50)$, were obtained for each segment. Each segment and shift with low signal quality was eliminated from final values.

2.4.4 | Covariates

Maternal covariates included BMI and two indicators of the degree of sleep-disordered breathing as detected by PSG: the apnea-hypopnea index (events/hour; AHI) and mean level of peripheral oxygen saturation (SpO2). Fetal sex was also analyzed.

3 | RESULTS

3.1 | Overnight trends

Data were collected for about an hour prior to sleep onset; maternal sleep commenced, on average, at 22:27 (*SD* = 68 min). Data collection continued through conclusion of the polysomnogram at approximately 06:00 when participants awakened spontaneously or the recording was terminated. Data display commences near 21:00, the point at which at least 60% of participants were monitored and/or had sufficient quality fHR data and terminates the following morning near 06:00 at which point less than 60% of participants were still being monitored. As a result, analysis was truncated at 05:00. Figure 2 provides sample size values for each hour of the recording.

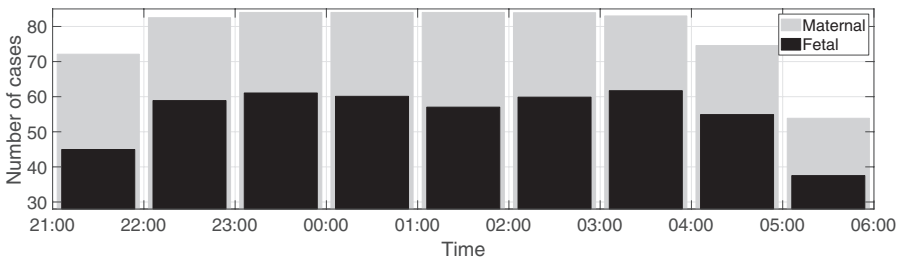

FIGURE 2 Maternal and fetal sample sizes with sufficient usable ECG data averaged over each hour of recording period. Much less artifact was present in maternal ECG than fetal ECG; maternal *n*s include the stacked upon fetal values.

The general trends for fetal (fHR) and maternal (mHR) heart rate during the overnight recording are illustrated in Figure 3. The declines in fHR and mHR evident in Figure 3 were confirmed by significant linear trends between 21:00 to 05:00: fHR t (27882) = −4.25, p < .001; mHR, t (38909) = −3.36, p < .001. Visual inspection suggested a potential change in slope of the decline for both fHR and mHR; this was established by insertion of a spline term revealing a significant reduction in the rate of the decline after 01:00 compared to earlier: fHR, t (27881) = 9.99, p < .0001; mHR, t (38908) = 5.36, p < .001. Note that in multilevel models, degrees of freedom are traditionally computed based on the number of measurements calculated across all participants; this yields a large number because data were sampled so frequently over a long period of time (Hox, 2010). However, these large values do not artificially inflate our ability to detect significance given the normal distribution of t-values in relation to probability levels as a function of sample size.

Variability in fHR (fHRV) and in mHR (mHRV) between 21:00 and 05:00 also declined linearly (Figure 4): fHRV, t (27793) = −1.72, p = .085; mHRV, t (38909) = −2.28, p < .005, although the decline in fHR attained only a trend level of significance. Nonetheless, as with heart rate, the slope of the decline in fHRV and mHRV flattened somewhat after 01:00: fHRV, t (27792) = 4.21, p < .001; mHRV, t (38908) = 5.87, p < .001.

Analysis of fetal sex, maternal BMI, and maternal SDB revealed no main effects of these covariates on fHR or fHRV level or change over time with one exception: higher maternal BMI was associated with faster fHR, t (27137) = 2.72, p < .005.

A second set of analyses was conducted using time series aligned to maternal sleep onset, as opposed to clock time, to evaluate the specific effect of sleep onset. fHR declined upon maternal sleep onset, from 140.4 bpm to 139.4 bpm, t (3521) = −4.37, p < .001, but without a corresponding change in fetal heart rate variability (fHRV).

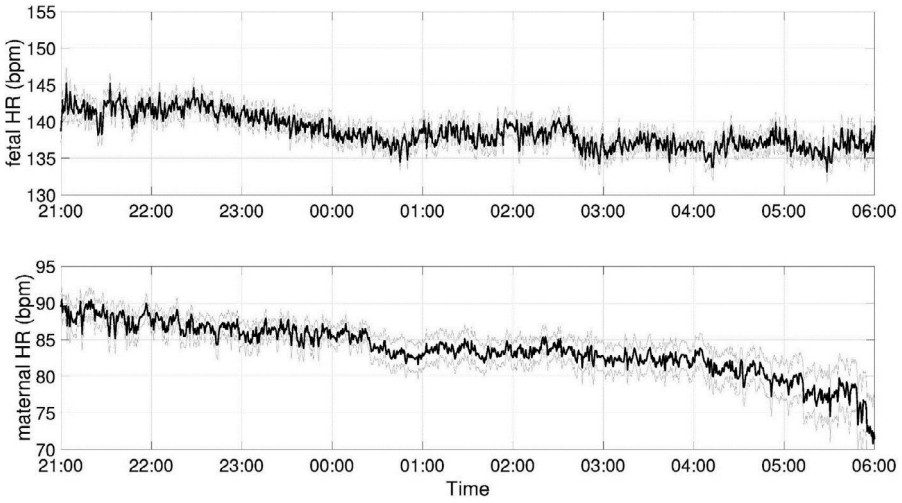

FIGURE 3 Trend in fetal and maternal heart rate (fHR/mHR) across all participants during recording period; standard errors noted by lighter lines surrounding mean (dark line) values.

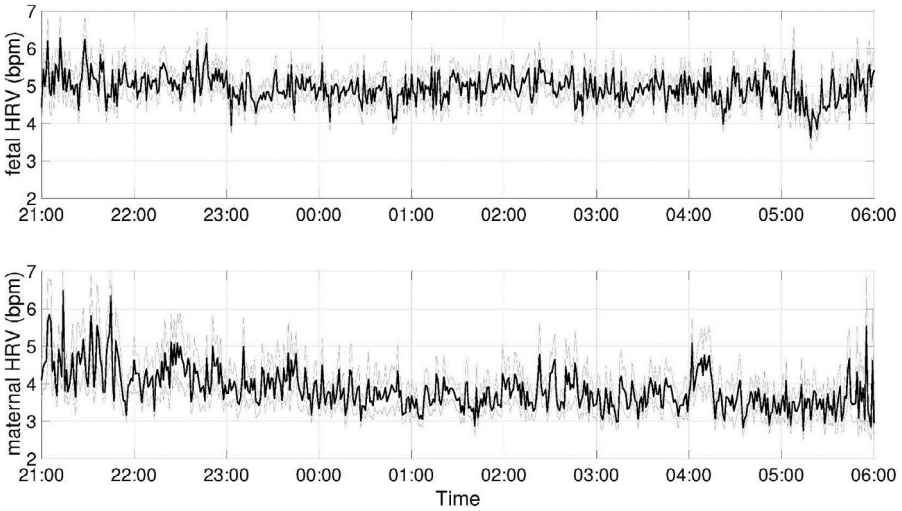

FIGURE 4 Trend in fetal and maternal heart rate variability (fHRV/mHRV) rate across all participants during recording period; standard errors noted by lighter lines surrounding mean (dark line) values.

mHR also declined, from 86.7 bpm to 84.5 bpm during the first 30 min of sleep, t (4864) = −8.78, p < .001 with an accompanying decrease in mHRV of 5.0 bpm to 3.3 bpm, t (4864) = 11.99, p < .001.

TABLE 2 Maternal sleep state duration (n = 84)

Variable	Total duration (minutes) *M* (*SD*)	Usable fetal data (minutes) *M* (*SD*)
Wakefulness prior to sleep onset	57.5 (41.8)	39.5 (34.7)
N1, transitional sleep	22.4 (16.6)	17.4 (14.9)
N2, lighter sleep	207.9 (50.0)	167.8 (60.9)
N3, slow wave sleep	61.7 (36.2)	51.9 (34.8)
REM sleep	53.5 (26.8)	44.3 (26.8)
Wakefulness after sleep onset	85.4 (58.5)	58.5 (49.8)
Total duration after sleep onset	430.9 (50.4)	339.9 (107.7)

3.2 | Comparison of mean values by maternal sleep stage

Mean duration values for maternal sleep stages are presented in Table 2. As expected, most time after sleep onset was spent in NREM sleep stages (63%), with N2, corresponding to lighter sleep, predominating (77%). As noted in Table 2, approximately 79% of fECG data was deemed suitable for analysis. Note that state-specific *n*s vary somewhat (*n*s range from 76 to 84) based on both unusable data and lack of expression of specific sleep stages (e.g., two participants failed to enter into N3). The amount of time women spent awake after sleep onset (WASO) varied, with a mean number of 19.2 (*SD* = 7.7) episodes. There was a modest negative association between maternal BMI and the amount of usable fetal data accrued during the night, r (82) = −0.28, p < .01.

Box plots presenting distributions, median values, 25th and 75th percentiles and confidence intervals (95%) for wakefulness prior to sleep onset (WPSO), maternal sleep stages N2, N3 and REM, and wakefulness after sleep onset (WASO) are provided for fHR and fHRV in Figure 5. To reduce the number of comparisons, and since

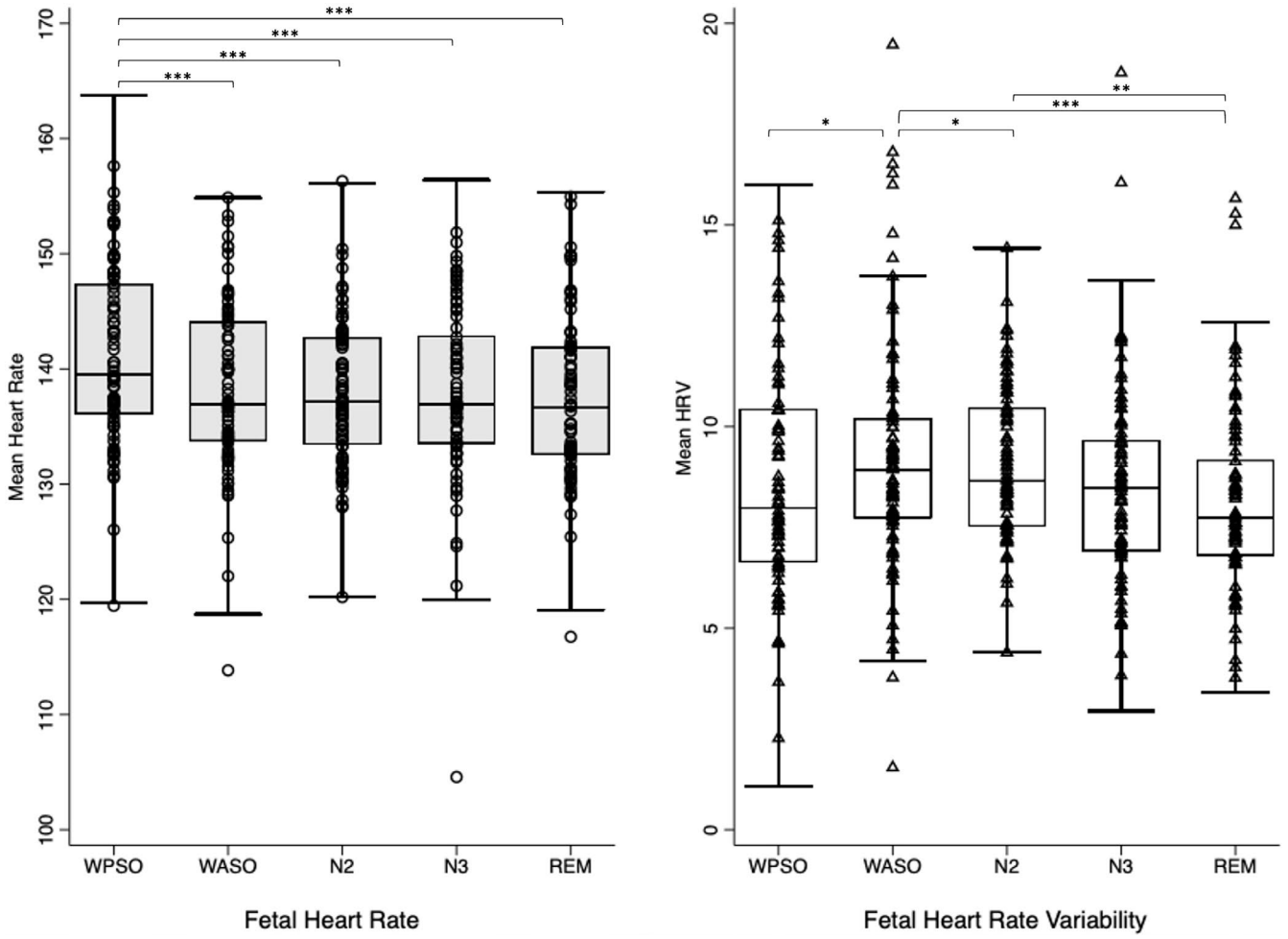

FIGURE 5 Fetal heart rate (fHR) and fetal heart rate variability (fHRV) including individual data points, median values, 25th and 75th percentiles and confidence intervals (95th percentile) during each maternal sleep stage, wakefulness prior to sleep onset (WPSO) and wakefulness after sleep onset (WASO). Notations at top indicate significant pairwise comparisons. *p < .05, **p < .01, ***p < .001.

N1 (transitional sleep) was relatively brief, it was not included in the analyses. Although medians are presented, statistical analyses were based on means (provided below), which exhibited similar patterns.

Overall fixed effects for fHR and fHRV were significant. Significant unadjusted pairwise comparisons (Figure 5) reveal decreases in fHR from WPSO, *M* = 141.1, to all maternal sleep stages: N2, *M* = 137.9, *coeff* −3.24, *z* = −4.40; N3, *M* = 138.7, *coeff* −2.92, *z* = −3.94; and to REM, *M* = 137.3, *coeff* −3.77, *z* = −5.07, all *p*s < .001, and wakefulness after sleep onset (WASO), *M* = 138.4, *coeff* −2.69, *z* = −3.65, *p* < .001. This reflects decreases ranging from −2.4 bpm to −3.8 bpm. fHR during maternal REM and NREM (N2 or N3) did not differ. For fHRV, the most consistent differences involved comparisons to WASO. fHRV was significantly higher during WASO, *M* = 9.3, than WPSO, *M* = 8.6, *coeff* .627, *z* = 2.00, *p* < .05, and also higher in WASO than during both N3, *M* = 8.5, *coeff* −.771, *z* = −2.51, *p* < .01 and REM, *M* = 8.2., *coeff* −1.09, *z* = −3.55, *p* < .001. The magnitude of the fHR and fHRV responses to WASO were not potentiated or ameliorated as a result of the amount of time pregnant women spent awake after sleep onset. fHRV during maternal REM sleep was significantly lower than during NREM N2, *M* = 9.1, *coeff* −.905, *z* = −2.94, *p* < .01.

Fetal heart rate accelerations (Figure 6) per hour ranged from a high of *M* = 7.3 (WASO) to a low of 5.7 (WPSO). Consistent with the findings for the continuous measure of fHRV, there were significantly more accelerations during WASO than WPSO, *coeff* 1.62, *z* = 2.55, *p* < .01, and fewer accelerations during both N3, *M* = 5.9, and REM, *M* = 5.9, than WASO, *coeffs* −1.40 and −1.50, *z*s = −2.24 and −2.40, respectively, *p*s < .05. Decelerations meeting criteria were relatively uncommon such that at least 70% of fetuses evidenced one or no decelerations per maternal sleep stage; in WPSO and REM sleep, that value was over 90%. As a result, they were not considered further for analysis.

Overall fixed effects for mHR and mHRV were also significant (Figure 7). mHR varied significantly between all pairwise comparisons *except* between WPSO vs WASO, and N3 versus REM sleep. All remaining comparisons were significant (*ps* < .001, except for WASO vs. REM, *p* < .05). Similarly, mHRV differed (*ps* < .001) between each pairwise comparison except between WPSO and N2 and REM, and between N2 and REM. mHRV peaked during wakefulness after sleep onset and was lowest in N3 sleep.

3.2.1 | Contribution of covariates to sleep stage analysis

Consistent with the previously reported finding based on full-night analysis, these analyses also detected a significant overall fixed effect between higher maternal BMI and faster fHR, *coeff* = .245, *z* = 2.48, *p* < .05. Neither AHI nor SpO2, the markers for sleep-disordered breathing, were significant covariates and no sex differences were detected.

3.3 | Maternal-fetal Coupling

3.3.1 | Time series analyses

Figure 8 provides results related to maternal-fetal coupling through cross-correlation functions at each lag from lag −50 s to +50 s for the initial period of maternal WPSO and aggregated periods of NREM, REM, and WASO. The overall cross-correlation and the associated

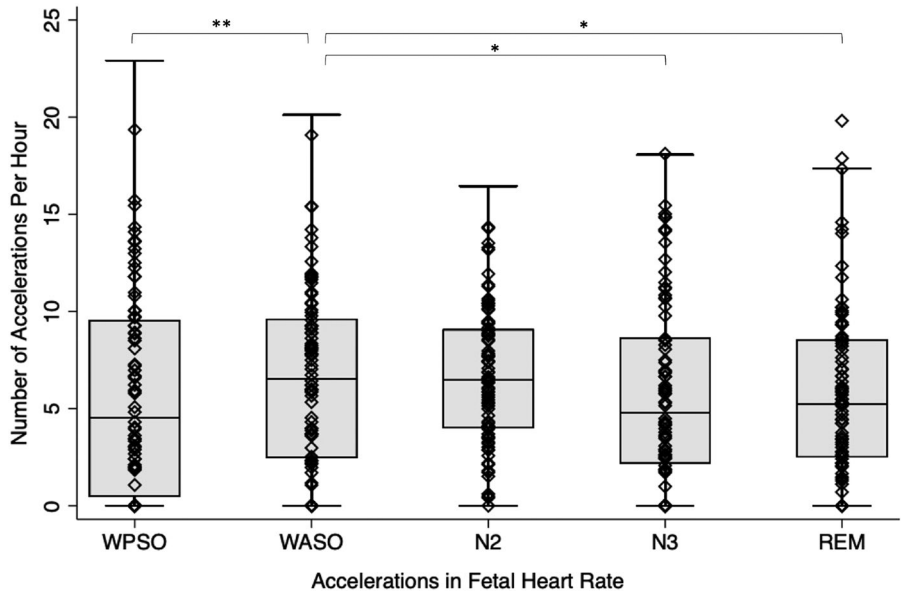

FIGURE 6 Accelerations in fetal heart rate (prorated for duration) including individual data points, median values, 25th and 75th percentiles and confidence intervals (95th percentile) during each maternal sleep stage, wakefulness prior to sleep onset (WPSO) and after sleep onset (WASO). Notations at top indicate significant pairwise comparisons. **p* < .05, ***p* < .01.

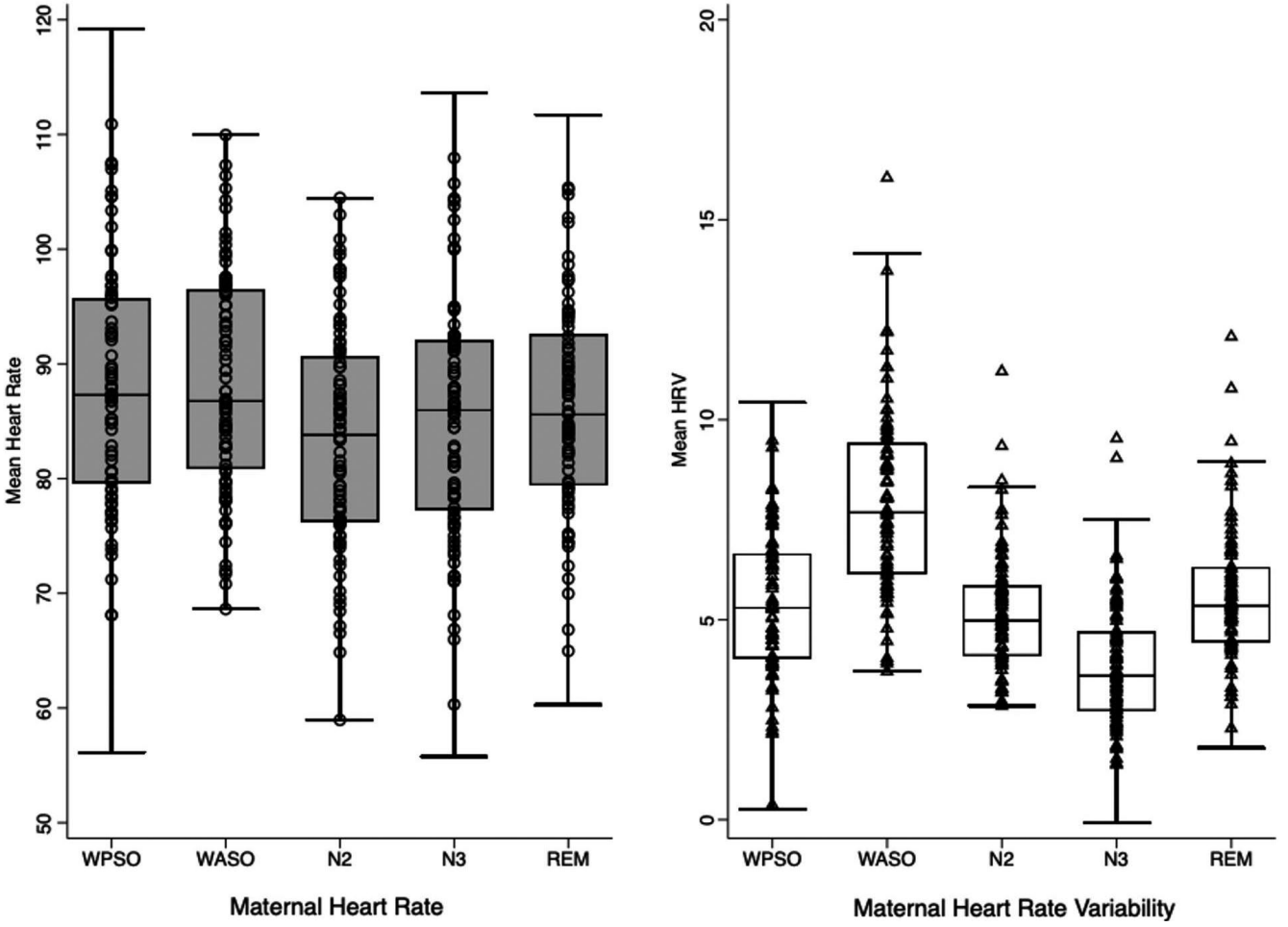

FIGURE 7 Maternal heart rate (mHR) and maternal heart rate variability (mHRV) including individual data points, median values, 25th and 75th percentiles and confidence intervals (95th percentile) during each maternal sleep stage, wakefulness prior to sleep onset (WPSO) and wakefulness after sleep onset (WASO). See text for information regarding significance of pairwise comparisons.

standard errors were plotted as the mean of all obtained correlations over all subjects and stages (or full night) with the associated standard error of the mean. Because mHR was fixed and fHR was shifted, values to the left of 0 indicate associations in which fHR precedes mHR, lag 0 reflects contemporaneous values, and those to the right of 0 reflect fHR following mHR. Means (*SD*) for available segments were: WPSO, *M* = 373 (3.6); deep sleep, *M* = 2,393 (7.8); REM, *M* = 470 (5.7); and WASO, *M* = 347 (7.8). Values in Figure 8 are based on the 5-minute threshold for stage continuity; analyses using 30-s designations were marked by instability and were not considered further.

Cross-correlation analysis findings conducted for the full night (not shown) are similar to the NREM (N2+N3) plots in Figure 8, as expected, since these stages dominated the recording. That plot, and those for WPSO and REM share similarities, with larger values after lags of ~ +10 s, shifted right. However, the values lack clear peak associations and range from a low of r = ~0.02 for NREM sleep to r = ~0.04 for WPSO, suggesting diffuse associations of very low magnitude. In contrast, although the coupling magnitude remains quite low during WASO, a clear peak lag of r = 0.05 is apparent at +3 s.

Analyses based on only instances in which either the maternal or fetal heart rate values exceeded the 25th and 75th quartile ranges, conducted to determine whether larger excursions in maternal and/or fetal heart rate are more likely to stimulate or reveal coupling, did not provide further insight and not considered further.

3.3.2 | Correlations of averaged values

In contrast to time series analyses, simple Pearson correlation coefficients based on aggregated mean values of fHR and mHR revealed modest but consistent significant associations between maternal-fetal heart rate levels over the course of the night, r (82) = 0.23, p < .05. Similar values were generated during NREM sleep stages N2, r (82) = 0.25 and N3, r (80) = 0.26, ps < .05, but not during REM sleep, r (79) = 0.08. fHR and mHR were unrelated during WPSO and WASO. Conversely, levels of fHRV and mHRV were unrelated when averaged over the night, r (82) = 0.13 and during each maternal sleep stage. However, higher fHRV was significantly associated with

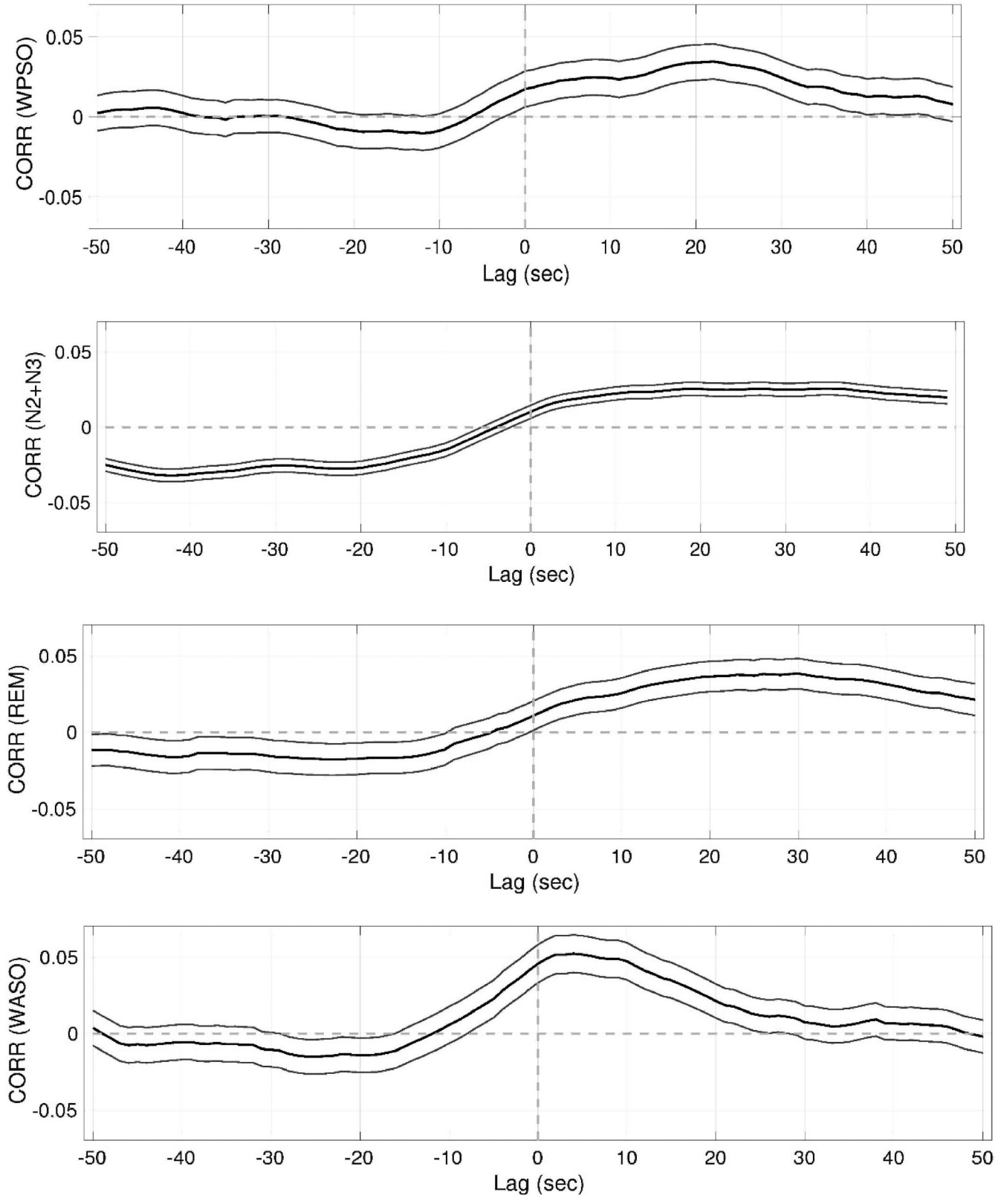

FIGURE 8 Maternal-fetal cross-correlation functions during the period of maternal wakefulness prior to sleep onset (WPSO) and periods of non-REM sleep (stages N2+N3), REM sleep, and waking after sleep onset (WASO). Within each figure, values (central black lines) reflect the correlation coefficients ±50 s such that Lag 0 is the contemporaneous association; lighter gray lines surrounding the central one reflect SE. Note that the smaller error bars for the NREM plot reflect more segments available for analysis.

higher mHRV during wakefulness prior to sleep onset, r (76) = 0.27, $p < .05$. Controlling for maternal covariates (BMI, AHI and SpO2) did not affect these associations.

4 | DISCUSSION

These findings concerning fetal heart rate during maternal sleep and evaluation of maternal-fetal coupling within and across sleep stages provide novel information on an aspect of the intrauterine milieu experienced by the human fetus which comprises nearly a third of gestation. Continuous recording of the fECG during polysomnography suggests that while the fetus may exhibit general trends in heart rate that reflect those of maternal heart rate, there is little support that the maternal heart rate per se serves to entrain the fetal heart rate. The most obvious correspondence was observed over the course of the night – both maternal and fetal heart rates declined linearly with a more precipitous decline prior to 01:00, reaching nadirs in the early morning hours prior to maternal waking. Heart rates for both also declined shortly upon maternal sleep onset. Similar parallels were observed for trajectories of maternal and fetal heart rate variability.

There were both consistencies and inconsistences between maternal and fetal heart rate patterns when compared across maternal sleep stages. As was true for mHR, fHR was lower in each maternal sleep stage than when women were awake prior to sleep onset. mHR varied across sleep stages, fHR did not. Of note, fHRV was lowest in maternal REM sleep but mHRV was highest in REM. Both fHRV and mHRV varied significantly between both or one NREM stage and REM, but their directions were often in opposition. In particular, fHRV was lowest in maternal REM sleep but mHRV was highest in REM. These findings failed to support our expectations that fHR and fHRV would be reduced during deepest maternal sleep (N3) and higher during maternal REM given the relative parasympathetic versus sympathetic tone underlying each. We conclude that while fetal heart rate responds to the advent of maternal sleep, it is not affected by the stages of maternal sleep. The same conclusion of lack of predictable associations between maternal sleep stages and fetal heart rate was also reached 40 years ago by Hoppenbrouwers et al., (1981). In contrast to their report, we did detect a difference between a maternal NREM state (N2) and REM in fetal heart rate variability, which may be the result of their small (n = 9) sample size, and awaits replication.

Women in this cohort spent more time awake after sleep onset (WASO) than in either N3 or REM, awakening approximately twice each hour, an observation consistent with the well-known sleep fragmentation that accompanies pregnancy. As a result, findings related to WASO are particularly important to understanding the maternal sleep context for the fetus. mHRV was higher in WASO than in any other sleep period, including compared to waking prior to sleep onset (WPSO); mHR in WASO showed a similar elevation, although was comparable to WPSO. An example of the nature of maternal heart rate fluctuations often observed in WASO can be seen in Figure 1 near 22:46. In contrast, fHR was lower in WASO than WPSO but, as with maternal measures, fHRV was higher during WASO than any other period, including WPSO. Accelerations in fHR were also higher in WASO than in maternal WPSO, REM and N3 sleep.

Together, these results suggest that when pregnant women awaken after sleep onset there are significant sympathetic activating effects to both mother and fetus. Acknowledged triggers for WASO episodes near term include physical discomforts, frequent micturition (Baratte-Beebe & Lee, 1999; Wilson et al., 2011), and intense dreams (Lara-Carrasco et al., 2014). Two other factors that may stimulate waking are uterine motility and fetal motor activity, both with known fetal cardio-activating effects (DiPietro et al., 2001; Sletten et al., 2016). Thus, the observed surge in continuously measured fHRV and larger excursions of fHRV (i.e., accelerations) may be generated not by the waking state per se, or the accompanying maternal heart rate response, but by intrauterine events that evoke both. Support for this is provided by the pattern observed for maternal-fetal coupling during WASO, which was distinct from any other period. During these episodes maternal-fetal heart rate showed some evidence of temporally based coupling within a 3-s lag.

It is tempting to ascribe circumstantial evidence to the existence of maternal-fetal heart rate coupling given the similarities in overall time trends and some stage-specific consistencies detected with multilevel modeling analyses of maternal and fetal heart rate values. However, our efforts to identify such coupling via the temporal associations during sleep revealed—with the exception of during WASO—consistently low cross correlation coefficients without evidence of a clear peak for NREM and REM sleep periods and WPSO. Results appeared similar whether analyzed over the entire observation period or within maternal sleep stages. The lack of clear peaks and overall appearance of the plots are similar to those for maternal-fetal heart rate reported previously based on 50-minute segments of data collected during the daytime (DiPietro et al., 2006). There is no clear consensus on how high values generated by cross-correlation methods based on high resolution data need to be to reflect a true association. Although generated by the same process at each lag, cross correlation coefficients are not interpreted in the same way as Pearson correlations, which quantify linear relations between two variables within a cohort of individuals. Here we have continuous signals in which many sources of variation, including stochastic variability in true lags, assumptions involving stationarity and linear relationships, and signal artifact can yield values considerably less than 1.0 even if two time series are highly coupled. While some of these issues are also relevant for Pearson correlation coefficients, their influenced is magnified in time series analyses which rely on multiple associations between these data series.

Yet, in the current sample, when averaged over longer intervals, heart rate was faster in fetuses of women with faster heart rates. This was observed during the full night and NREM stages. Such correspondence was expected and has been reported by others. However, the putative assumption of a causal association between the two was not supported by time series analysis. Despite

differences in population characteristics, length of recording period, and the context of maternal sleep, we reiterate the same conclusion (DiPietro et al., 2006) - that any observed correspondence between maternal and fetal heart rate measures described to this point must be generated by secondary processes that mediate both. Identification of these processes remains elusive. Fetal heart rate entrainment via maternal cardiac patterning has been an appealing candidate because, in addition to its expression of a range of core maternal processes, the maternal heart rate is prominently featured in the fetal auditory environment. To date the only reported synchrony has been observed between fetal motor activity and maternal skin conductance, and, to a lesser extent, maternal heart rate. Although the magnitudes of those cross-correlations were also relatively low, confidence in them was bolstered by clear and consistent peak lags of 2 to 3 s across multiple gestational periods during the second half of gestation. Moreover, in both instances, fetal activity preceded maternal activation, which suggests a physiological pathway (DiPietro et al., 2006).

4.1 | Implications for fetal ontogeny

While it is accepted that the broader maternal circadian cycle serves to entrain the fetal clock (Lunshof et al., 1998; Mirmiran et al., 1992; Peirano et al., 2003), and as with more temporally linked aspects of maternal-fetal coupling, the underlying mechanisms remain unclear. Neuro-hormonal regulatory mechanisms are under consideration (Bates & Herzog, 2020) but autonomic processes are also likely contributors. This consistent finding, based on data collected at varying levels of temporal resolution, duration, and methodology indicates that this is a core feature in the regulatory development of the fetal autonomic nervous system. However, after birth and without continued maternal input, this cycle is no longer immediately evident, apparent in the neonate's typical lack of compliance with light-dark cycles. There remains little understanding of the processes through which maternal circadian entrainment occurs or the potential role of independently developing fetal oscillators (Mirmiran et al., 2003; Stark et al., 1999). This study does not provide insight to either possibility.

Fragmented sleep is normative during pregnancy, and characterized by frequent episodes of wakefulness that increase as gestation advances. Longitudinal (Lee et al., 2000) and cross-sectional studies comparing pregnant women to non-pregnant controls routinely observed poorer sleep efficiency, less slow wave and REM sleep, and more transitory awakenings among pregnant women (Izci-Balserak et al., 2018; Ladyman & Signal, 2018; Rimpilä et al., 2017; Wilson et al., 2011). Our results also confirmed findings from studies of non-pregnant adults that spontaneously or exogenously generated nocturnal arousals result in a transitory surge of cardiovascular activity (Trinder et al., 2003). Here we show that this response appears to persist in pregnancy, which is otherwise often associated with a blunting of physiological responsivity (DiPietro et al., 2012; Ekholm et al., 1993). Thus the implications of this normative maternal sleep patterning for the fetus should be considered within the context of ontogeny. Frequent night awakenings may serve to routinely perturb the developing fetal nervous system by eliciting sympathetic activation, followed by parasympathetic toning. Although pregnancy-induced sleep disturbances are an unwelcome phenomenon for pregnant women, it is possible that oppositional strategies that maximize well-being on the part of both fetus and pregnant woman are in play, as has been proposed in regards to regulation of hemodynamic properties of pregnancy (Haig, 1993). Within this broader framework of mutually adaptive regulatory processes, a classic study of maternal bedsharing with 3-month-old infants revealed that bedsharing provoked 30% more frequent maternal awakenings after sleep onset at the cost of less non-REM sleep; results were interpreted within the context of the resultant benefits to the infant and the intricacies of maternal-infant regulatory synchrony (Mosko et al., 1997). It has been long-speculated that the disrupted sleep of late term pregnancy prepares the pregnant woman for the demands of caring for an infant lacking in circadian cyclicity (Baratte-Beebe & Lee, 1999). We have previously suggested that the observed maternal sympathetic activation that occurs in response to fetal motor activity, whether felt or unfelt, may serve a similar maternal preparatory function (DiPietro et al., 2006).

Although it seems reasonable to expect that there might be an upper threshold at which repetitive fetal disruption following maternal nocturnal awakenings are deleterious to fetal development, a recent meta-analysis failed to establish effects of poor maternal sleep quality (as opposed to sleep disordered breathing) on adverse outcomes including fetal growth, preterm birth or stillbirth although there are relatively few studies on these potential consequences (Warland et al., 2018). However, in one study, self-reported sleep quality was predictive of preterm birth in a sub-sample of African-American participants; a relationship that appears to be mediated by pro-inflammatory cytokines (Blair et al., 2015). This suggests that there may be differential susceptibility to poor sleep during pregnancy that is amplified by systemic inequities and racial disparities in health. Preterm birth is marker of disruption to the intrauterine milieu and may portend more subtle consequences to fetal neurodevelopment.

These results are based on pregnancies characterized by maternal obesity. While obesity during pregnancy is not an uncommon phenomenon in the United States with national prevalence estimates of 39.7% for women of childbearing age (Hales et al., 2020), generalizability to the full population of pregnant women must be made with caution. Obesity related disorders, such as gestational diabetes and pregnancy-induced hypertension may contribute independently to maternal and fetal cardiac measures. We could not analyze these disorders separately because the rates were quite low in the study population and incidence varied strongly with maternal BMI, which was controlled in analyses. With respect to the broader sleep context, characteristics of sleep architecture (i.e., distribution of NREM and REM stages, duration of WASO) were consistent with PSG values reported in other non-obese pregnant populations (Izci-Balserak et al., 2018; Ladyman & Signal, 2018). Although higher maternal BMI

was associated with faster fetal heart rate during sleep but not waking periods, the overnight patterns of decline in both maternal and fetal heart rate paralleled those reported by others on non-selected samples, and BMI was unrelated to the sleep stage comparisons. However, there is a report of reduced fetal heart rate variability in obese women as compared to non-obese women (Voegtline et al., 2016). Although we did not find a gradient between BMI and fHRV in this study, we cannot rule out that comparisons with a non-obese control group might reveal other complexities.

The second threat to generalizability is the likelihood that maternal sleep during laboratory-based polysomnography and fetal monitoring disrupted maternal sleep. As a result, the distribution of maternal sleep stages observed here may be different than experienced during routine sleep at home, presenting a novel environment to the fetus which may have affected the fetal response. Sleep tends to be less fragmented on the second night of consecutive polysomnography as adaptation occurs; such "first night" effects have been documented in non-pregnant adult women (Virtanen et al., 2018b). Interestingly, despite differences in sleep cycling, no differences in heart rate variability were detected in that study (Virtanen et al., 2018a). To fully estimate this threat to generalizability of the current study findings, serial nightly recordings would be necessary but the cost and incremental burden on pregnant women would have made this study infeasible. Early work on sleep during pregnancy found few differences in sleep characteristics over two consecutive night polysomnograms (Brunner et al., 1994) and the most recent study to incorporate an adaptation night during full polysomnography with pregnant women detected no significant differences in sleep characteristics between the first and second nights (Lee et al., 2000). While we cannot discount the possibility that the fetal response to maternal sleep would be different during a non-monitored night, as discussed earlier, pregnancy itself generates significant maternal sleep fragmentation so any additional effect conferred by monitoring would only be a matter of degree.

The relatively recent development of a commercially available fetal ECG monitor affords the ability to collect fetal cardiac pattern data over extended periods of time and has generated a spate of new research. Reports include those focused on the relation between maternal sleep position and fetal heart rate measures during the night (Lucchini et al., 2020; Stone et al., 2017) as well as more general diurnal trends and influences (Kapaya et al., 2016; Sletten et al., 2016, 2018) However, in general, prolonged fetal ECG monitoring remains a frustrating endeavor. Despite significant expertise in fetal monitoring, we were unable to collect a signal of sufficient quality in 20% of originally eligible participants, although usable data for those individuals who could be monitored averaged near 80%. This success rate is comparable to other reports that include this information (e.g., Graatsma et al., 2009; Kisilevsky & Brown, 2016; Lucchini et al., 2020). It is unclear what makes signal quality good in one individual but poor or absent in another; maternal BMI accounted for only 8% of the variance in signal loss.

This is the first study to document the fetal heart rate response to maternal stages of sleep and wakefulness before and after maternal sleep onset. Its focus on cardiac measures as indicative of autonomic responsiveness is necessarily narrow given technological constraints. Sleep affects multiple regulatory systems within the pregnant woman and, in turn, maternal sleep likely affects multiple fetal systems. This report has focused on detailing group effects of maternal sleep on the fetus, providing the foundation for consideration of individual differences within maternal-fetal pairs and implications for subsequent development. Much remains to be learned about the mechanisms that mediate the complex maternal-fetal relationship.

CONFLICT OF INTEREST

No author has a financial conflict of interest with the work reported here.

AUTHOR CONTRIBUTIONS

DiPietro: design, planning, study conduct, data analysis, manuscript preparation; Raghunathan: study conduct, data analysis, manuscript preparation; Wu: data analysis and manuscript preparation; Bai: data consolidation and analysis; Watson: planning, study conduct, data management, recruitment; Sgambati: data consolidation and study conduct; Henderson: design, planning, recruitment; Pien, design, planning, conduct, manuscript preparation.

DATA AVAILABILITY STATEMENT

Maternal-fetal polysomnography data are available from the corresponding author upon request.

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